# General

## Guideline Title

Guidelines on oral anticoagulation with warfarin - fourth edition.

## Bibliographic Source(s)

Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, Kitchen S, Makris M, British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol. 2011 Aug;154(3):311-24. [111 references] PubMed

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Baglin TP, Keeling DM, Watson HG, British Committee for Standards in Haematology. Guidelines on oral anticoagulation (warfarin): third edition--2005 update. Br J Haematol 2006 Feb;132(3):277-85.

# Recommendations

## Major Recommendations

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Indications for Warfarin and Recommended Target International Normalized Ratio (INR)

Venous Thromboembolism (VTE)

- First episodes of VTE should be treated with an INR target of 2.5 (1A).
- Warfarin used for treatment of VTE should be introduced along with parenteral anticoagulation (1A) which should continue for at least 5 d and until the INR is ≥2 for at least 24 h (1C).
- Recurrent VTE whilst anticoagulated and within the therapeutic range should be managed by increasing the INR target to 3.5 (2C).

Antiphospholipid Syndrome (APS)

- The target INR should be 2.5 in patients with APS (1A).

Atrial Fibrillation (AF)

- Patients with AF who require warfarin for the prevention of cardio-embolic stroke should have an INR target of 2.5 (1A).

Cardioversion

- Patients undergoing elective cardioversion should be anticoagulated with warfarin for at least 3 weeks prior to and 4 weeks post cardioversion with a target INR of 2.5 (2C). To minimize cardioversion cancellations due to low INRs on the day of the procedure a target INR of 3.0 can be used prior to the procedure.

Valvular Heart Disease and Prosthetic Valves

*Mitral Stenosis or Regurgitation*

- Patients with mitral stenosis or regurgitation who have atrial fibrillation (1A) or a history of systemic embolism (1A) or left atrial thrombus (1A) or an enlarged left atrium (2C) should receive warfarin with an INR target of 2.5.

*Mechanical Prosthetic Heart Valves*

The recommended target INRs for mechanical heart valves are given in the table below.

Table: Recommended target INRs for mechanical heart valves (2B) [adapted from Vahanian et al., European Heart Journal, 2007:28, 230–268]

| Prosthesis Thrombogenicity* | INR target No patient risk factors | INR target Patient-related risk factors† |
|---|---|---|
| Low | 2.5 | 3.0 |
| Medium | 3.0 | 3.5 |
| High | 3.5 | 3.5‡ |

*Prosthesis thrombogenicity: Low: Carbomedics (aortic position), Medtronic Hall, St Jude Medical (without silzone); Medium: Bjork-Shiley, other bileaflet valves; High: Starr-Edwards, Omniscience, Lillehei-Kaster.

†Patient-related risk factors for thrombosis: Mitral, tricuspid or pulmonary position; Previous arterial thromboembolism; Atrial fibrillation; Left atrium diameter >50 mm; Mitral stenosis of any degree; Left ventricular ejection fraction <35%; Left atrial dense spontaneous echo contrast.

‡Was 4.0 in Vahanian et al (2007).

- In situations where an embolic event occurs during anticoagulation within target, elevation of the INR target or the addition of anti-platelet drugs should be considered (2C).

*Bioprosthetic Heart Valves*

- Patients with a bioprosthesis in the mitral position should receive 3 months of anticoagulation with warfarin with an INR target of 2.5 (1B).
- Patients with a bioprosthetic valve and a history of systemic embolism should have at least 3 months of anticoagulation with warfarin with an INR target of 2.5 (1C).
- Patients with a bioprosthetic valve and left atrial thrombus at surgery should receive warfarin until the clot has resolved with an INR target of 2.5 (1C).
- Patients with bioprosthetic valves and other prothrombotic risk factors, such as atrial fibrillation and low ventricular ejection fraction, should receive warfarin with an INR target of 2.5 (1C).

Peripheral Vascular Disease

- Patients with intermittent claudication should not routinely be treated with anticoagulants (1A).
- Patients who suffer acute arterial embolism and proceed to embolectomy should be considered for long-term anticoagulation with warfarin with an INR target of 2.5 (2C).

Myocardial Infarction and Cardiomyopathy

- When warfarin is used following myocardial infarction, the INR target for anticoagulation is 2.5 (2A).
- Patients with dilated cardiomyopathy who are anticoagulated to prevent systemic embolism should have an INR target of 2.5 (2C).

Duration of Anticoagulation for Pulmonary Embolism (PE) and Lower Limb Deep Vein Thrombosis (DVT)

Duration of Initial Anticoagulation

- Patients with proximal DVT or pulmonary embolism should be treated for at least 3 months (1A).
- If a diagnostic strategy that identifies isolated calf vein DVT is employed, treatment of such clots can be restricted to 6 weeks (1A).
- Patients with cancer-associated VTE should initially be treated for 6 months with therapeutic dose low molecular weight heparin (LMWH) rather than warfarin (1A).

Continued Anticoagulation Beyond the Initial Period of 3 Months

- Long-term anticoagulant therapy is not recommended in patients with VTE provoked by surgery (1B).
- Long-term anticoagulant therapy is not recommended in patients with VTE provoked by non-surgical transient trigger factors (1B).
- Patients with unprovoked proximal DVT or pulmonary embolism should be considered for long-term anticoagulation, taking into account information that may help predict risk of recurrence and risk of bleeding in the individual patient (2B).
- Long-term anticoagulant therapy is not recommended in patients with VTE confined to the calf (i.e., not extending into the popliteal vein) (1A).

Initiation of Treatment

Rapid Induction Regimens for Patients with Acute Thrombosis

- Overall there is no evidence to suggest a 10 mg loading dose is superior to a 5 mg loading dose. However in the elderly lower initiation doses or age-adjusted doses may be more appropriate as they lead to fewer high INRs (2B).
- There is insufficient evidence to warrant genotype-guided initiation as response to a standard dosing algorithm can equally accurately predict maintenance dose (2B).

Induction of Anticoagulation in Outpatients with Atrial Fibrillation

- For outpatients who do not require rapid anticoagulation a slow-loading regimen is safe and achieves therapeutic anticoagulation in the majority of patients within 3–4 weeks (2C).

Peri-operative Anticoagulation

- Pre-operative bridging carries a low risk of bleeding but the use of post-operative bridging requires careful consideration due to the high risk of bleeding. The authors recommend that post-operative bridging should not be started until at least 48 h after high bleeding risk surgery (1C).
- Patients with VTE more than 3 months earlier can be given prophylactic dose low molecular weight heparin (or a suitable alternative) rather than bridging therapy (2C).
- Patients with low risk AF (no prior stroke or transient ischaemic attack [TIA]) do not require bridging therapy (2C).
- Patients with a bileaflet aortic mechanical heart valve (MHV) with no other risk factors do not require bridging (2C).
- Patients with a VTE within the previous 3 months, patients with AF and previous stoke or transient ischaemic attack or multiple other risk factors, and patients with a mitral mechanical heart valve should be considered for bridging therapy (2C).

Management of Bleeding and of High INR in the Absence of Bleeding

Major Bleeding

- All hospitals managing patients on warfarin should stock a licensed four-factor prothrombin complex concentrate (PCC) (1C).
- Emergency anticoagulation reversal in patients with major bleeding should be with 25–50 u/kg four-factor PCC and 5 mg intravenous vitamin K (1B).
- Recombinant factor VIIa is not recommended for emergency anticoagulation reversal (1B).
- Fresh frozen plasma produces suboptimal anticoagulation reversal and should only be used if PCC is not available (1C).

Non-Major Bleeding

- Anticoagulation reversal for non-major bleeding should be with 1–3 mg intravenous vitamin K (1B).

INRs >5.0 and >8.0 in Non-Bleeding Patients

- Patients with an INR >5.0 but who are not bleeding should have 1–2 doses of warfarin withheld and their maintenance dose should be reduced (1B). The cause of the elevated INR should be investigated (1C).

- Patients with an INR >8.0 should receive 1–5 mg of oral vitamin K (1B).

Emergency Surgery for Patients on Warfarin

- For surgery that requires reversal of warfarin and that can be delayed for 6–12 h, the INR can be corrected by giving intravenous vitamin K. For surgery that requires reversal of warfarin and which cannot be delayed, for vitamin K to have time to take effect the INR can be corrected by giving PCC and intravenous vitamin K. PCC should not be used to enable elective or non-urgent surgery (2C).

Head Injury in Patients on Warfarin

- All patients on warfarin presenting to Accident and Emergency departments with head injury should have their INR measured as soon as possible (1C).
- A lower threshold for performing a head computed tomography (CT) scan should be used for patients on warfarin (2C).
- Patients on warfarin presenting with a strong suspicion of intracerebral bleed should have their anticoagulation reversed before the results of any investigations (2C).

Management of Sub-Therapeutic Anticoagulation in the First Month After Acute VTE

- The authors suggest that bridging therapy be considered if the INR becomes significantly sub-therapeutic within the first month of an acute VTE (2C).

Combination Warfarin and Antiplatelet Therapy

Patients on Antiplatelet Therapy who Develop an Indication for Warfarin

- Patients receiving an anti-platelet agent as primary prophylaxis for cardiovascular disease (CVD) on developing an indication for warfarin should stop their antiplatelet agent (1B).
- Patients with peripheral artery disease or previous ischaemic stroke on antiplatelet therapy should stop this agent if warfarin is commenced (1B).
- Patients on aspirin or clopidogrel as secondary prophylaxis with stable ischaemic heart disease (often defined as >12 months following acute myocardial infarction) should stop their antiplatelet agent while being treated with warfarin (2B).
- Patients on a single antiplatelet agent <12 months following an acute coronary syndrome (ACS), who require to start warfarin therapy should continue aspirin therapy until 12 months post ACS, unless they are regarded as having a high bleeding risk (2B).
- Patients on aspirin and clopidogrel, following an ACS or stent placement, who develop an indication for warfarin should be carefully assessed for bleeding risk and discussed with their cardiologist, with a view to introducing warfarin and minimizing the duration of triple therapy (2C).
- When combined warfarin and single antiplatelet agent are indicated, consideration should be given to use of aspirin given the higher bleeding risk associated with clopidogrel (2C).

Patients on Warfarin Who Develop an Indication for Antiplatelet Agents

- Patients requiring a coronary artery stent, should be considered for bare metal stent (rather than drug-eluting stent) which would only necessitate triple therapy for 4 weeks, followed by aspirin and warfarin to 12 months (2B).
- Patients who do not undergo percutaneous coronary intervention (PCI) should be considered for 4 weeks triple therapy, after which clopidogrel should be stopped, and aspirin continued for a further 11 months (2C).

Anticoagulant Monitoring and Dose Adjustment

Drug Interactions

- For patients on warfarin, computer-assisted dosing is superior to manual dosing (1A).
- Self-testing and self-management of warfarin is associated with improved anticoagulant control but may not be suitable for most patients (2B).
- All patients on warfarin must have a written record of their results and dose changes (2C).
- In individuals with an unstable INR, supplementing the diet with 100–150 μg vitamin K may improve anticoagulant control (2B).
- All patients on warfarin who are prescribed a drug that may interact with it should have an INR performed after 3–5 d (2C).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

## Clinical Algorithm(s)

None provided

# Scope

## Disease/Condition(s)

Conditions requiring oral anticoagulation therapy, including:

- Venous thromboembolism (VTE)
- Antiphospholipid syndrome (APS)
- Atrial fibrillation (AF)
- Conditions requiring cardioversion
- Valvular heart disease and prosthetic valves
- Peripheral vascular disease
- Myocardial infarction and cardiomyopathy
- Pulmonary embolism (PE)
- Deep vein thrombosis (DVT), including cancer-associated DVT

## Guideline Category

Management

Prevention

Risk Assessment

Treatment

## Clinical Specialty

Cardiology

Critical Care

Family Practice

Hematology

Internal Medicine

Pulmonary Medicine

Surgery

Thoracic Surgery

## Intended Users

Physician Assistants

Physicians

## Guideline Objective(s)

To provide healthcare professionals with clear guidance on the indications for and management of patients on warfarin

## Target Population

People in the United Kingdom with conditions requiring anticoagulation prophylaxis or therapy

## Interventions and Practices Considered

1. Warfarin dose based on international normalized ratio (INR)
2. Duration of anticoagulation for pulmonary embolism and lower-limb deep vein thrombosis
3. Induction of anticoagulation (i.e., loading doses)
4. Peri-operative anticoagulation (bridging therapy)
5. Reversal of anticoagulation for emergency surgery
6. Management of bleeding or high INR in the absence of bleeding
7. Bridging therapy for sub-therapeutic anticoagulation in the first month after an acute venous thromboembolism
8. Combination warfarin and antiplatelet therapy
9. Management of head injuries
10. Anticoagulant monitoring and dose adjustment (manual dosing, computer-assisted dosing, patient self-management, vitamin K intake, patient records, drug interactions)

Note: The following were considered but not recommended: genotype-guided initiation as response to a standard dosing algorithm, recombinant factor VIIa for emergency anticoagulation reversal, long-term anticoagulation in selected situations.

## Major Outcomes Considered

- Rates of thrombosis, myocardial infarction, and stroke
- Bleeding rates
- Mortality

# Methodology

## Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

The guidance is updated with reference to relevant publications since 2005. Publications known to the writing group were supplemented with additional papers identified by searching PubMed for publications in the last 5 years using the key word warfarin and limits clinical trial, randomized control trial, meta-analysis, humans, core clinical journals, and English language.

## Number of Source Documents

Not stated

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

## Description of the Methods Used to Analyze the Evidence

Not stated

## Methods Used to Formulate the Recommendations

Expert Consensus

### Description of Methods Used to Formulate the Recommendations

The writing group was selected to be representative of United Kingdom (UK) based experts. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology.

### Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

### Cost Analysis

Computerized dosing has been shown to increase the overall percentage time for which patients are in their target international normalized ratio (INR) range and in some studies to reduce the frequency of testing of patients. Furthermore, it has been shown to significantly reduce the risk of bleeding and thromboembolic events and overall is a more cost-effective option to manual dosing.

### Method of Guideline Validation

External Peer Review

Internal Peer Review

### Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 United Kingdom (UK) haematologists, the British Committee for Standards in Haematology (BCSH), the British Cardiovascular Society and the British Society for Haematology Committee and comments incorporated where appropriate.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

- Reduction in thromboembolisms and other morbidities
- Reduction in excess bleeding
- Reduction in delays of cardioversion and surgical procedures

- Improved survival rates

### Potential Harms

Not stated

## Qualifying Statements

### Qualifying Statements

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Living with Illness

Staying Healthy

### IOM Domain

Effectiveness

Patient-centeredness

Safety

## Identifying Information and Availability

### Bibliographic Source(s)

Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, Kitchen S, Makris M, British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol. 2011 Aug;154(3):311-24. [111 references] PubMed

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2006 Feb (revised 2011 Aug)

## Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

## Source(s) of Funding

British Committee for Standards in Haematology

## Guideline Committee

Haemostasis and Thrombosis Task Force

## Composition of Group That Authored the Guideline

*Task Force Members*: David Keeling, Oxford Radcliffe Hospitals, Oxford; Trevor Baglin, Addenbrooke's Hospital, Cambridge; Campbell Tait, Glasgow Royal Infirmary, Glasgow; Henry Watson, Aberdeen Royal Infirmary, Aberdeen; David Perry, Addenbrooke's Hospital, Cambridge; Caroline Baglin, Addenbrooke's Hospital, Cambridge; Steve Kitchen, Royal Hallamshire Hospital, Sheffield, UK; Michael Makris, Royal Hallamshire Hospital, Sheffield, UK

## Financial Disclosures/Conflicts of Interest

All authors made a declaration of interests to the British Committee for Standards in Haematology.

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Baglin TP, Keeling DM, Watson HG, British Committee for Standards in Haematology. Guidelines on oral anticoagulation (warfarin): third edition--2005 update. Br J Haematol 2006 Feb;132(3):277-85.

## Guideline Availability

Electronic copies: Available from the British Committee for Standards in Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

## Availability of Companion Documents

None available

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on May 22, 2008. This NGC summary was updated by ECRI Institute on February 14, 2012. The updated information was verified by the guideline developer on February 17, 2012. This summary was updated by ECRI Institute on March 10, 2014 following the U.S. Food and Drug Administration advisory on Low Molecular Weight Heparins.

## Copyright Statement



# Disclaimer

## NGC Disclaimer